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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,011	07/16/2003	Julie D. Saba	200116.405C1	1654

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EXAMINER
CHOWDHURY, IQBAL HOSSAIN

ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,011	SABA, JULIE D.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14, 16, 19-23, 26-27 and 30-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14, 16, 19-23, 26-27 and 30-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a CIP of US application 10/348,052 filed 01/17/2003 and 10/053510 filed 1/17/2002 and US Patent 6,830,881, which claim benefit of provisional application 60/349,582 filed on 1/17/2002.

The amendment filed on 12/1/2006, amending claims 12-14, 16, 19-23, 26-27, 30-31, and canceling claims 1-11, 15, 17-18, 24-25 and 28-29 is acknowledged.

Claims 12-14, 16, 19-23, 26-27 and 30-31 are currently pending and under consideration in the instant application.

Applicants' arguments filed on 12/1/2006 have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

New-Claim Objections

Claims 12, 16, 20 and 27 are objected to at the recitation "wherein said at least one gene comprises a -------(DPL1) gene and a -------(LCB4) gene". The phrase does not make scientific / grammatical sense. It should be "wherein said at least one gene comprises a -------(DPL1) gene or a -------(LCB4) gene". Examiner requests correction.

Maintained - Claim Rejections - 35 U.S.C. § 112

Previous rejection of claims 12-14, 16, 19-23, 26-27 and 30-31 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter, which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been described at length in previous Office Actions. Applicant's amendments to claims 12-14, 16, 19-23, 26-27, 30-31, and canceling claims 1-11, 15, 17-18, 24-25 and 28-29 and arguments have been fully considered but are not deemed persuasive for the following reasons.

Claims are directed to a method of identifying an agent that modulates sphingolipid metabolism by culturing a mutant Saccharomyces cerevisiae strain comprising null allele of at least one gene encoding DPL1 or LCB4 or YSR2 gene and wherein said mutant strain of yeast is transformed with genus of DNA molecules encoding polypeptide SK1 or a human SK including all variants, mutants and recombinants. The specification teaches the structure of only few representative species of such DNAs. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding SK proteins.

Applicants argue that they have cancelled several claims and amended the remaining claims to specifically recite "the mutant yeast strain comprises a null allele of at least one gene encoding a component of a sphingolipid pathway that results in an altered activity level of at least one sphingolipid pathway component, wherein said at least one gene comprises a DPL1 gene and a LCB4 gene and wherein said mutant strain of yeast has been genetically altered to express at least one non-endogenous SK1, and wherein the mutant yeast strain exhibits growth inhibition in the presence of sphingosine" and request to reconsider of the amended claims and withdrawal of the rejection.

Applicant's arguments, and cancellation of claims and amendments to claims have been fully considered but are not deemed to be persuasive to overcome the rejection on Written description issues.

Examiner acknowledges the amendment in claims 12-14, 16, 19-23, 26-27 and 30-31 however maintains that the amendment does not give enough structural information non-endogenous SK1, which is required for fulfilling written description requirements. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of species disclosed. For inventions in an unpredictable art, adequate written description of a genus, which embraces widely, variant species, cannot be achieved by disclosing only one species within the genus. The genus of non-endogenous SK proteins used in the method recited in claims 12-14, 16, 19-23, 26-27, 30-31, is structurally diverse as it encompasses many

polypeptides with respective activity having different structures. As such, the disclosure solely of functional features present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus. Therefore, the rejection is maintained.

Maintained - Claim Rejections - 35 U.S.C. § 112

Previous rejection of Claims 12-14, 16, 20-22, 26-27 and 30 under 35 U.S.C. 112, first paragraph, enablement requirement, is maintained. This rejection has been described in length in previous Office Action. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that amended claims specifically recite "the mutant yeast strain comprises a null allele of at least one gene encoding a component of a sphingolipid pathway that results in an altered activity level of at least one sphingolipid pathway component, wherein said at least one gene comprises a DPL1 gene and a LCB4 gene and wherein said mutant strain of yeast has been genetically altered to express at least one non-endogenous SK, and wherein the mutant yeast strain exhibits growth inhibition in the presence of sphingosine..." and requested to reconsider of the amended claims and withdrawal of the rejection.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 12-14, 16, 20-22, 26-27 and 30 on enablement issue. The examiner acknowledges the amendment to the claims but disagrees with the applicant's contention that the scope of the claimed invention is adequately described. As mentioned in the previous Office Actions, the specification (claims 12-14, 16, 20-22, 26-27 and 30), while being enabling for a method of identifying an agent that modulates sphingolipid metabolism using a

mutant Saccharomyces cerevisiae strain comprising a null allele of the endogenous DPL1 gene and/or LCB4 gene and/or YSR2 gene and transformed with a non-endogenous SK such as that encoding either SEQ ID NO: 19, 20, 21, 28 or 29, does not reasonably provide enablement for a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway and expressing any gene encoding a any or all non-endogenous sphingosine kinase (SK) including mutants, variants and recombinants of human SK or that of SEQ ID NO: 19, 20, 21, 28 or 29. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of non-endogenous SK1 genes including mutants and variants broadly used in the methods of the claims. The scope of the claimed invention is very broad in the context of using any mutant strain and "altered activity of at least one component of sphingolipid pathway" and the genus of SK1 genes including mutants and variants used in the claimed method as explained above.

The claims read on use of any SK1 genes including mutants and variants from any source without any structural limitations. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. For example, Branden et al. (1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple

property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes. However, in the instant case the disclosure is limited to the species used of SEQ ID NO: 19, 20, 21, 28 or 29 as non-endogenous SK in the claimed method. The specification clearly requires that one of ordinary skill in the art know or be provided with guidance for making of selecting which of the infinite number of said SK genes can be used and which mutant and variant has the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway including DPL1 gene or LCB4 gene or YSR2 gene and expressing any gene encoding a non-endogenous sphingolipid pathway component. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166

USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of a component a sphingolipid pathway including DPL1 gene or LCB4 gene or YSR2 gene and expressing any gene encoding a non-endogenous sphingolipid pathway is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Therefore, for the reasons above, and as described previous Office action, the rejection is maintained.

Maintained- Claims Rejections- 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Previous rejection of Claims 12-16, 19-23, 26-227, and 30-31 under 35 U.S.C. 103(a) as being unpatentable over Lanterman et al. (Biochem J. 1998 Jun 1; 332 (Pt 2): 525-31), Kim et al. (Genetics. 2000 Dec; 156(4): 1519-29) and in view of Melendez et al. (Gene. 2000 Jun 13; 251(1): 19-26 and GenBank Accession No. AF266756, created 6/1/2000) is maintained.

Instant claims are drawn to a method of identifying an agent that modulates sphingolipid metabolism by culturing any mutant yeast strain comprising a null allele of any gene encoding a component a sphingolipid pathway or any DPL1 gene or any LCB4 gene or any YSR2 gene and expressing any gene encoding a non-endogenous sphingolipid pathway component or any sphingosine kinase.

Applicants argue that the PTO fails to establish a *prima facie* case of obviousness. (See en re Mayne, 104 F.3d 133, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997). PTO has the burden of showing a prima facie case of obviousness and the Examiner must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. Applicants also argue that when

rejection of claims depends upon a combination of prior art references, a teaching, motivation, or suggestion to combine the references must exist. (See In re Rouffet, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)). Applicants further argue that at the time of filing the present application, the cited combination of references would not have motivated a person having ordinary skill in the art to arrive at the claimed invention with the requisite reasonable expectation of success, and Applicant submits that Lanterman et al. merely describe the characterization of sphingosine kinase activity in Saccharomyces cerevisiae. Furthermore, applicants argue that nowhere does said reference teach the presently disclosed mutant yeast strains expressing a non-endogenous SK protein as recited in the instant claims and the Action relies improperly on Kim et al. and Melendez et al. to overcome this deficiency. Applicants also argue that Kim et al. merely describe the further characterization of the biological role of phosphorylated long chain bases in yeast and Kim et al. fail to cure the deficiencies of Lanterman et al., in particular by providing no actual teaching with regard to the use of non-endogenous SK in a screening assay. Melendez et al. merely teach the molecular cloning and characterization of the human SK cDNA with no teaching of the use of such a cDNA as a non-endogenous gene in a yeast screen and, in fact, no teaching whatsoever of any screening methods. Applicant submits that the Action employs inappropriate and selective hindsight where the allegation of obviousness is asserted to derive from a reason in the art other than knowledge provided by Applicant's disclosure. In re Dow Chemical Co., 837 F.2d 469; 5 USPQ2d 1529 (Fed. Cir. 1988). Absent the teachings of the present application, the documents cited in the Action simply fail to render the claimed invention obvious to the person having ordinary skill in the art, who would have no basis for reasonably believing that the instant

methods could be successfully practiced. In alleging that there would have been motivation to combine the references to arrive at a method to screen modulators of sphingolipid metabolism, at best, the Action asserts nothing more than that it would have been "obvious to try." Such an assertion cannot be regarded as a conclusory finding that the claimed invention is obvious, and in fact fails to support a prima facie case of obviousness. In re Eli Lilly & Co., 902 F.2d 943; 14 USPQ2d 1741 (Fed. Cir. 1990). Accordingly, Applicant submits that the primary and secondary references, taken individually or for what they teach as a whole, do not teach or suggest the claimed invention and therefore, the claimed invention would not have been obvious to the ordinarily skilled artisan at the time of filing.

Applicant's amendments, and arguments have been fully considered but are not deemed persuasive to overcome the rejection on obviousness issue.

As described previous office action, Lanterman et al. teach a method of identifying an agent using yeast strain by measuring the production of sphingosine-1-P, which reflects the activity of sphingosine kinase, whether the kinase is inhibited or not in presence or absence of the candidate agent. Lanterman et al. also teach the creation of mutant strain, which comprises a null allele of DPL1 (dihydrosphingosine phosphate lyase) gene and an active LCB4 (kinase of sphingolipid pathway). Lanterman et al. further teach that the Δ DPL mutant yeast is extremely sensitive to sphingosine owing to its inability to degrade S-1-P and in presence of extracellular D-erythro-sphingosine results in accumulation of S-1-P, which is toxic to the cells and inhibits cell growth. However, double mutants of Δ DPL and Δ LCB4 do not have growth inhibitory effect of extracellular D-erythro-sphingosine because kinase mutant yeast strain comprising Δ LCB4 does not produce S-1-P molecule. It would have been obvious to one of ordinary skill in

the art to use this system to identify an agent, which would inhibit kinase, which produces S-1-P as Lanterman et al. clearly show that the ΔDPL1 are growth inhibited only in the presence of an active sphingosine kinase. Lanterman et al. do not teach mutant yeast strain comprising null allele of endogenous YSR2 phosphatase gene and transforming said mutant strain with non-endogenous human SPHK1 gene encoding human sphingosine kinase 1, which is complimentary to LCB4 of yeast sphingosine kinase, which is mutated in the mutant yeast strain and expressing said SPHK1 gene.

Kim et al. disclose a method of analyzing sphingolipid metabolism in a mutant S. cerevisiae having disruption mutants of DPL1 (lyase), or LCB4 (kinase), or YSR2 (phosphatase) or in combination and assay methods of sphingolipid metabolism. Kim et al. also disclose that when DPL1 and YSR2 genes are mutated in yeast strains, it results in the enhancement of sphingosine-1-phosphate (S-1-P) level either in the culture medium or inside the cell to growth inhibitory levels but that ΔDPL1-LCB4-YSR2 triple mutant does not accumulate toxic levels of S-1-P. Kim et al. further teach that over expression of LCB4 i.e. kinase in triple mutant yeast strain ΔDPL1-LCB4-YSR2 results in the 500 fold accumulation of S-1-P than control, which is also extremely growth inhibitory to the mutant cells comprising triple mutant ΔDPL1-LCB4-YSR2 yeast strain, but over-expression of LCB4 in wild type yeast strain do not have such effects. As such Kim et al. clearly show that the triple mutant strains growth inhibited only in the presence of an active heterologous sphingosine kinase gene. Kim et al. do not teach method of screening agents by using mutant yeast system and transforming said mutant strain with non-endogenous human SPHK1 gene encoding human sphingosine kinase 1 and expression.

Melendez et al. teach a human sphingosine kinase (SPHK1), molecular cloning, and expression in host cells, functional characterization and tissue distribution. Melendez et al. also teach that sphingosine-1-phosphate (SPP), the product of sphingosine kinase, is an important signaling molecule with intra- and extracellular functions. Melendez et al. further teach an assay method to identify an inhibitor such as D,L-threo-dihydrosphingosine or N,N-dimethyl-sphingosine, which inhibit the human SPHK1 kinase and subsequently alter the sphingolipid metabolism.

Contrary to applicants arguments Lanterman et al. and Kim et al. indeed teach an assay method of sphingosine kinase (SK) by which an activator or inhibitor of SK can be evaluated in terms of S-1-P formation. Lanterman et al. and Kim et al. also teach yeast strain null of DPL1 or LCB4 or YSR2 or double or triple mutant strain, although do not teach using a human SK. However, Melendez et al. teach a human SK and an assay method to identify an inhibitor such as D,L-threo-dihydrosphingosine or N,N-dimethyl-sphingosine, which inhibit the human SPHK1 kinase and subsequently alter the sphingolipid metabolism.

Thus, It would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Lanterman, Kim and Menendez et al. to assay for inhibitors of human sphingosine kinase 1 (SPHK1) gene to identify an agent by using mutant ΔDPL1 and ΔLCB4 or a ΔDPL1, YSR2, LCB4 yeast strain transformed with said human SPHK1 gene, which modulates sphingolipid metabolism by monitoring either 1) the growth of mutant ΔDPL1, ΔLCB4 or ΔDPL1, YSR2, LCB4 yeast strain, as Lanterman et al. and Kim et al. each show that these strains are growth inhibited in the presence of an active sphingosine kinase such as SPHK, or 2) the concentration of S-1-P, which would decrease if the agents were

active. It would have been obvious to one of ordinary skill in the art to identify an agent which alters the growth of mutant yeast strain or accumulation S-1-P concentration to identify an agent would be expected to prevent human diseases like cancer and muscular disorders in which S-1-P enhances cell proliferation, calcium mobilization or Raf/MEK/ERK signaling pathway or decreases apoptosis.

One of ordinary skill in the art would have been motivated to use human sphingosine kinase 1 (SPHK1) gene instead of yeast sphingosine kinase gene in order to obtain an agent or modulator of the human sphingosine kinase to use that agent as a therapeutic measure against human diseases like cancer and muscular disorders.

One of ordinary skill in the art would have a reasonable expectation of success because use of non-endogenous human gene to isolate agents or modulators, in a mutant yeast strain having disruption of endogenous genes are customary and widely used in the art.

Thus, for the reasons above and as discussed previous office action, the rejection is maintained.

Conclusion

No claim is in condition for allowance.

Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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